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AB A specific liver cell membrane receptor, hepatic binding protein (HBP), is necessary for the uptake of asialoglycoproteins by hepatocytes. Isolated perfused rat liver pre-infused with anti-HBP IgG exhibited 80% reduction in asialoorosomucoid (ASOR) uptake, but no change in bilirubin uptake,

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LIVER METASTASIS

Basic aspects, detection and management

edited by

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PREFACE

E. CADY

Hepatic metastases present one of the major therapeutic challenges of cancer patient management, for it is the destruction of vital organ function that makes cancer fatal, not local tumor growth. The process of tumor cell dislodgement from the primary cancer, their spread through the lymphatic and hematogenous channels, their lodgement in distant sites, and their subsequent progressive growth tax our comprehension and frustrate our therapies. The proceedings of this International Congress on Hepatic Metastasis address these aspects of metastases to the liver, and predominatly focus on metastatic colon cancer because of its frequency, its prominent hepatic only pattern of spread, and enticing preliminary data about prevention and control of small subsets of the afflicted population. Predictably, the "false technologies" of Dr. Lewis Thomas that involve surgical, radiotherapeutic and chemotherapeutic attack on these metastases after elaborate diagnostic studies take precedence because of the clinical imperatives of sick patients. This is displayed in the preponderance of papers and interest in various diagnostic scanning techniques by means of radioisotopes, radiographically useful dyes, biochemical markers, interest in developing accurate staging systems to categorize patients for therapeutic comparisons, and interest in elaborate, and expensive, technology to increase the effectiveness of chemotherapeutic agents that are of limited benefit with simple intravenous administration.

Behind this clinical enthusiasm, however, lies the research to develop the "true technology," in Thomas' words, that will prevent such clinical catastrophies as hepatic metastases. The first inkling of such a "true technology" in liver cancer is the recent development of hepatitis immunization to prevent subsequent hepatoma in endemic areas of the world. In hepatic metastases from colon cancer, several

RECEPTOR-MEDIATED ENDOCYTOSIS BY NORMAL AND PROLIFERATING HEPATOCYTES AND LIPOSOMAL DRUG DELIVERY

ALLAN W. WOLKOFF, M.D., RICHARD J. STOCKERT, Ph.D. AND PHILIP S. SCHEIN, M.D.

Receptor-mediated endocytosis is a process common to many species and cell types. One of the best characterized systems in which this process occurs is that of the hepatocyte receptor for asialoglycoproteins (1). This receptor was first described by Ashwell and Morell in studies of plasma disappearance of ceruloplasmin (2). In these studies performed in rats, they determined that native ceruloplasmin had a circulating half-life of 55 hours. Like virtually all mammalian plasma proteins, with the exception of albumin, ceruloplasmin is a glycoprotein consisting of a protein core with complex carbohydrate side-chains attached via aspartate residues. The terminal carbohydrate in these chains is sialic acid; the penultimate is galactose. Removal of sialic acid, exposing galactosyl residues, resulted in a reduction in circulating half-life to minutes rather than hours. Plasma clearance of asialoceruloplasmin as well as most other asialoglycoproteins represents uptake into hepatocytes. This uptake is mediated by a specific liver cell membrane receptor, hepatic binding protein (HBP) (3).

HBP is a membrane glycoprotein which has been solubilized in detergent and purified from rat, rabbit and human liver. As demonstrated in studies performed in isolated perfused rat liver, HBP is necessary for uptake of asialoglycoproteins by hepatocytes (4). In these studies, rat liver was first perfused with 100 mg of non-immune goat IgG (Figure 1). Following IgG infusion, a mixture of ^{125}I-Asialoorosomucoid (ASOR), ^{3}H-Bilirubin and ^{131}I-Albumin was injected as a small bolus into the portal vein. Albumin was used as a non-transported reference. Its extracellular space of distribution is that of bilirubin, which circulates bound to it, and is similar to

that of ASOR, a protein of comparable molecular weight. Following injection, all effluent coming from the hepatic vein was collected in aliquots every 1-2 seconds without recirculation. In this way, uptake of bilirubin and ASOR during a single pass through the liver could be quantitated. Following this study, anti-HBP IgG was infused and the study repeated (Figure 2). Analysis revealed that uptake of ASOR was reduced by over 80% following anti-HBP infusion, while bilirubin uptake did not differ from control. These studies also revealed that uptake of bilirubin which occurs by facilitated diffusion rather than by endocytosis is independent of uptake of ASOR.

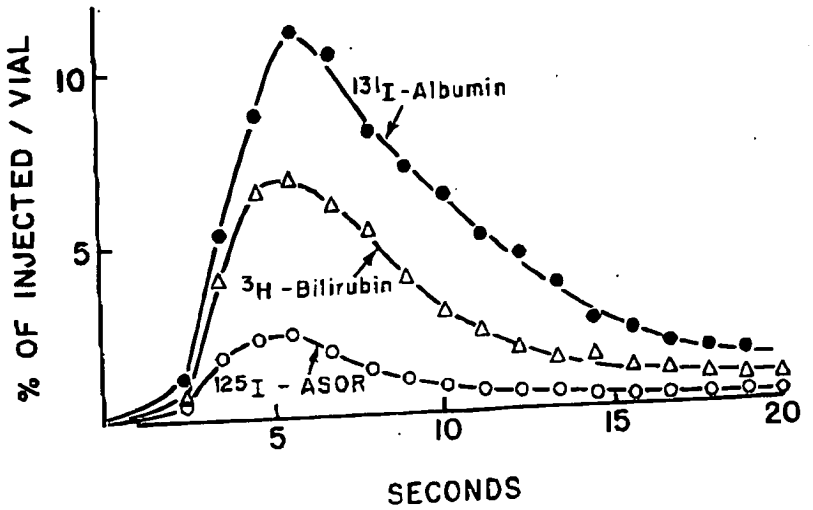

Figure 1: Hepatic venous outflow patterns of ^{131}I-Albumin, ^{3}H-Bilirubin, and ^{125}I-Asialoorosomucoid (ASOR) following simultaneous injection into the portal vein of an isolated perfused rat liver following pre-infusion of non-immune goat IgG. (Reprinted from reference 4 with permission).

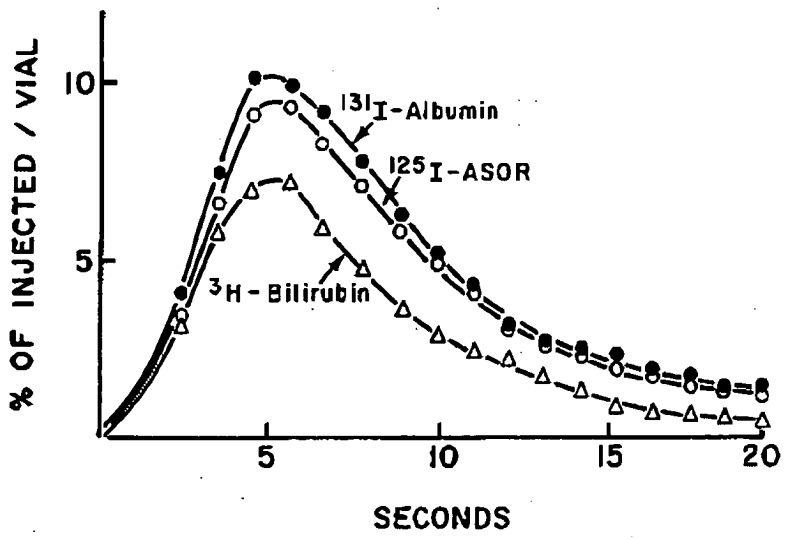

Figure 2: The same liver as in Figure 1 was then infused with anti-HBP IgG and the transport study was repeated. There was a marked reduction in uptake of ^{125}I-ASOR as indicated by increased recovery, while uptake of ^{3}H-Bilirubin was unchanged. (Reprinted from reference 4 with permission).

Newer studies have revealed that endocytosis of ASOR following binding to HBP is a complex event (5). Following binding of ligand to cell surface HBP, the ligand-receptor complex is internalized into a prelysosomal compartment that has been termed the endosome. The endosome interior becomes acidified resulting in dissociation of ligand and receptor (6). The ligand and receptor segregate from each other; receptor eventually recycles to the cell surface, while ligand enters lysosomes where degradation takes place. Recent studies have identified specific inhibitors of these steps (Figure 3).

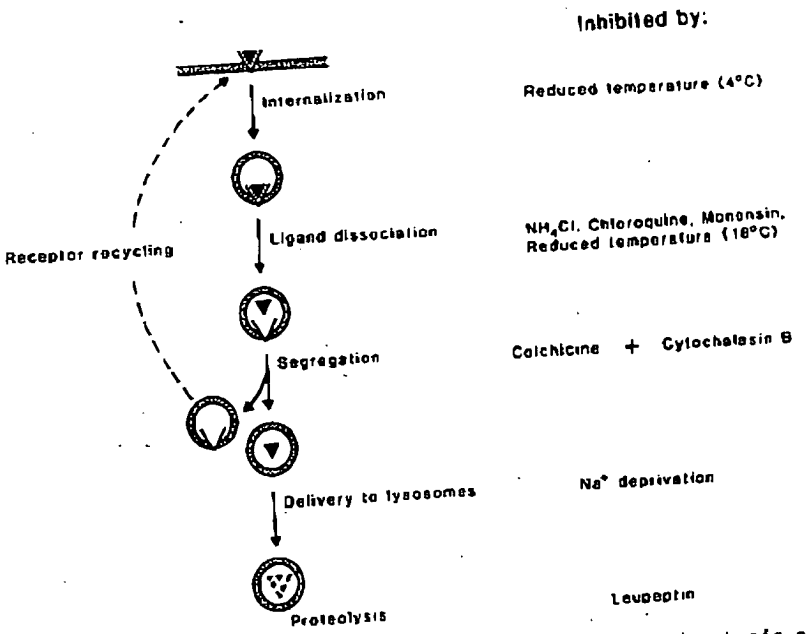

Figure 3: Schematic diagram of receptor-mediated endocytosis of asialoglycoproteins and its inhibitors. Based on these and other studies, five discrete steps in uptake and catabolism can be quantitated. Inhibitors of each of these steps have been identified. Inhibitors are assigned on the basis of their most proximal site of action as a wave of prebound ligand moves through the pathway. (Reprinted from reference 5 with permission).

The liver cell plasma membrane plays an important role in receptor-mediated endocytosis. Because the liver cell surface may undergo marked changes during proliferation, we studied transport of ASOR and bilirubin by regenerating rat liver (7). The rat hepatocyte divides approximately once per year, and mitosis in hepatocytes is infrequently seen in normal liver (8). Following two-thirds hepatectomy, rapid cellular proliferation occurs throughout the remaining liver remnant, and is associated with expression of oncofetal antigens (9-11). Studies performed with hepatocytes in culture suggest that hepatocyte replication is associated with modulated expression of several intracellular and secreted proteins including ligandin, pyruvate kinase, and α-1-fetoprotein (12). Altered liver cell plasma membrane function during regeneration has also been suggested. Studies of the interaction of plasma membrane,

prepared from regenerating liver, with insulin and glucagon revealed an increased number of insulin receptors and reduced number of glucagon receptors (13). Amino acid uptake by hepatocytes was found to be increased several-fold during liver regeneration (14). This finding which may be due to an altered plasma membrane transport mechanism, is blocked by pretreatment with colchicine, a microtubule disrupter. Changes in other liver cell plasma membrane enzymes occur in regeneration, including a doubling of (Na^+-K^+)-ATPase activity and a reduction in glucagon-stimulated adenyl cyclase activity (15).

As a measure of specific hepatocyte function, transport of ^{3}H-Bilirubin and ^{125}I-ASOR was determined using the single-pass indicator dilution method in the isolated perfused regenerating liver (7). This method permits quantitation of uptake rates independent of hepatic mass. Results were compared to those obtained in sham-operated rats. As seen in Figure 4, liver weight increased progressively with time after two-thirds hepatectomy, and returned to normal by six days. Uptake of ^{3}H-Bilirubin and ^{125}I-ASOR fell by over 50% and 80%, respectively, reaching a nadir at the time of greatest cell proliferation (Figure 5). Uptake returned to normal by six days. These studies of transport of anions and asialoglycoproteins during liver regeneration revealed functional maturation similar to that seen during development.

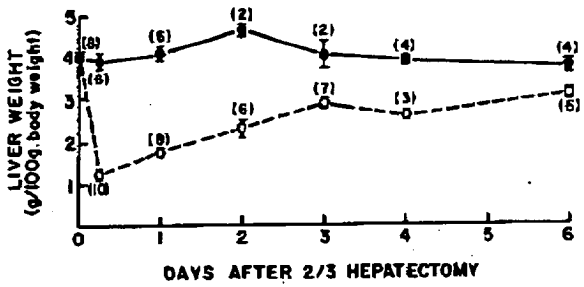

Figure 4: Liver weight in sham-operated rats (●) and two-thirds hepatectomized rats (○) at various times after surgery. (Reprinted from reference 7 with permission).

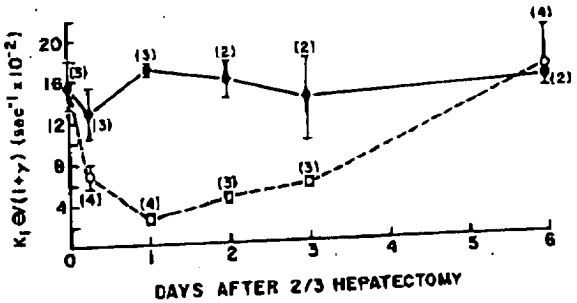

Figure 5: Influx rate of ^{125}I-ASOR ($k_1\theta/(1+\gamma)$) in perfused liver from sham-operated (●) and partially hepatectomized rats (○). Rate constants were calculated from indicator dilution curves. Similar results were obtained in studies of ^{3}H-Bilirubin transport. (Reprinted from reference 7 with permission).

That hepatocellular proliferation alone is not responsible for the transport alterations seen during liver regeneration was demonstrated in perfused liver from rats pretreated with nafenopin (16). Nafenopin (2-methyl-2p-(1,2,3,4,-tetrahydro-1-naphthyl) phenoxy propionic acid) is a hypolipidemic drug which induces rapid liver growth characterized by hepatocellular hypertrophy and hyperplasia similar to that seen during regeneration (17-20). After nafenopin treatment, the liver has morphologic features of regeneration including proliferation of smooth endoplasmic reticulum, enlargement of peroxisomes and Golgi, and dilated and tortuous bile canaliculi (21,22). Despite a 40% increase in liver weight 24 hours after two days of nafenopin, there was no change in transport of bilirubin or ASOR, unlike results seen in regeneration (Figure 6). However, uptake of the water soluble organic anions, BSP and conjugated bilirubin was reduced by 50% (Figure 6). These studies suggest that hepatocellular proliferation alone is not responsible for the transport alterations seen during liver regeneration. Nafenopin effectively unmasks differences in uptake of bilirubin and other more water soluble organic anions such as sulfobromophthalein and conjugated bilirubin, suggesting that their uptake mechanisms are partially independent. As discussed below, reduced uptake of ASOR during liver regeneration is a consequence of reduced numbers of cell surface receptors for this ligand. Whether there are analagous alterations in organic anion interaction with liver cell surface membranes during regeneration or after nafenopin-treatment remains to be determined.

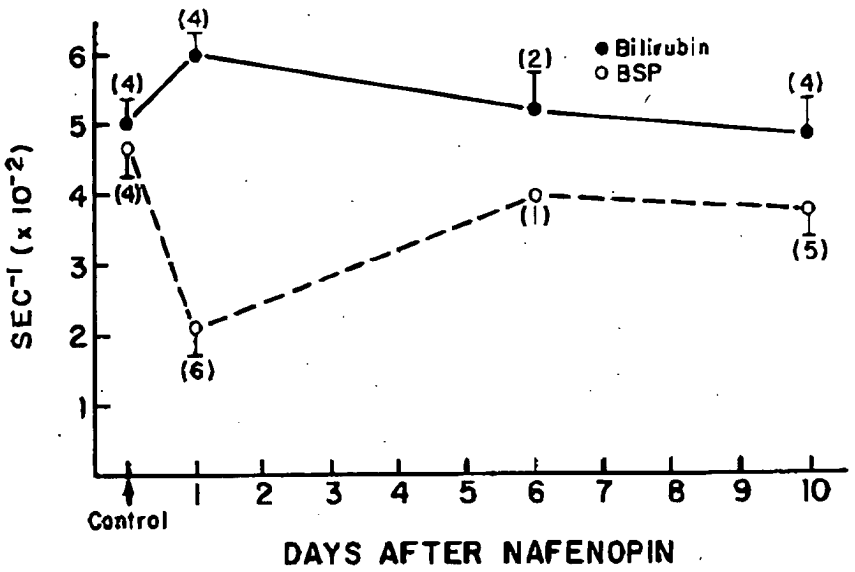

Figure 6: Influx of ^{3}H-Bilirubin and ^{35}S-BSP in isolated perfused liver of rats pretreated with nafenopin. There was no change in influx of either compound in corn oil fed controls. Despite the marked proliferative response similar to that seen in regeneration, influx of bilirubin remained constant, as did influx of ASOR. In contrast, BSP influx was significantly reduced.

Reduced uptake of ASOR during liver regeneration could be due to a number of factors. That it is due to reduced levels of HBP on the liver cell surface, however, has been demonstrated (23). In these studies, isolated hepatocytes were prepared from livers at various times after two-thirds hepatectomy. Binding of ^{125}I-ASOR to the cell surface or to solubilized cell homogenates was determined as was uptake and degradation of this ligand (Figures 7 and 8). Results were compared with identical studies performed in cells obtained from sham-operated rats. Similar to results in perfused liver, there was reduced uptake of ASOR by hepatocytes obtained during the period of active cell proliferation. This was accompanied by an 80% loss of receptor from the cell surface. Total cell receptor, as determined in the solubilized homogenates, was normal (Figure 8).

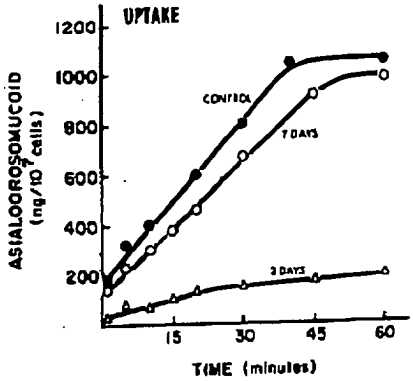

Figure 7: Uptake of ASOR by isolated hepatocytes obtained from sham-operated rats or rats 2 days (Δ) or 7 days after two-thirds hepatectomy. Similar to results in perfused liver, uptake is reduced during the proliferative phase of regeneration. (Reprinted from reference 23 with permission).

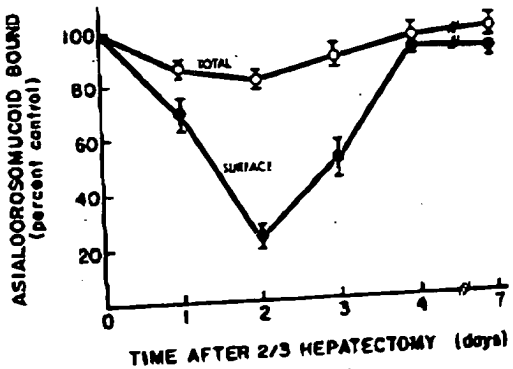

Figure 8: Binding of ASOR by intact hepatocytes (●) and cell homogenates (○) at various times after two thirds hepatectomy. During the time of active cell proliferation, there was an 80% loss of receptor from the cell surface. (Reprinted from reference 23 with permission).

The modulation of liver cell HBP content seen during regeneration is similar to that which has been observed in the mouse during development (24). As seen in Figure 9, fetal mice have no detectable receptor until the nineteenth day of gestation, and develop normal adult levels by 5 days postpartum. Maternal liver has a tripling of HBP activity in the last trimester, with a fall to normal levels shortly after birth.

These studies suggested that hepatocytes during regeneration entered a state of "dedifferentiation". Other studies have revealed altered liver cell membrane enzyme activities during hepatocarcinogenesis (25). Based on these data, Stockert and Becker (26) studied HBP content of rat liver following exposure to the chemical carcinogen AAF (N-2-acetylaminofluorene). As has been described, this drug induces formation of neoplastic nodules and hepatocellular carcinoma in rat liver (27). These nodules can be dissected free of other liver tissue and studied biochemically. HBP, as assayed by specific binding of ^{125}I-ASOR, was reduced by almost 70% in neoplastic nodules and by 95% in areas of hepatocellular carcinoma.

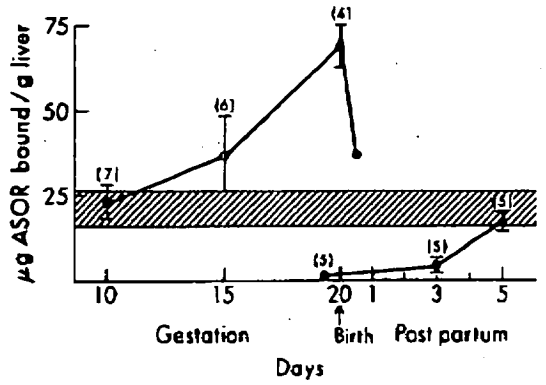

Figure 9: Asialoglycoprotein receptor binding activity in pregnancy, fetal and neonatal development. The hatched area indicates control male and virgin female mouse liver activity. Pregnant mice (●) have supranormal receptor activity while developing mice (●) do not have detectable receptor activity until the nineteenth day of gestation. (Reprinted from reference 24 with permission).

These studies have suggested potential new directions in treatment of hepatocellular carcinoma. Exciting studies along these lines have recently been performed by Wu and colleagues (28) in studies of methotrexate. The lack of specificity for neoplastic tissue which results in injury to normal as well as malignant cells, has limited the clinical usefulness of this drug. In addition, hepatotoxicity frequently complicates treatment with high levels of methotrexate. These investigators synthesized a covalent conjugate of folinic acid with asialofetuin with the goal of directing this methotrexate antagonist to receptor-bearing cells, sparing them from methotrexate toxicity. Less differentiated cells not containing HBP, would be killed by methotrexate.

Two cultured cell lines were used for these studies. One was a relatively undifferentiated human hepatocellular carcinoma line, PLC/PRF/5, which lacks HBP. The other was a more differentiated human hepatocellular carcinoma line, HepG2. This is the only cultured cell line which has been found to express HBP. As seen in Figure 10, PLC/PRF/5 receptor negative cells were killed by methotrexate both in the presence and absence of the asialofetuin-folinic acid conjugate. Methotrexate also killed HepG2 cells, but this effect was eliminated by adding the folinic acid conjugate to the medium. Thus, these studies reveal specific rescue of differentiated cells based upon the presence of a specific receptor on the cell surface. They may have important implications in the design of clinical chemotherapeutic protocols.

A similar line of investigation has been conducted on liposome delivery of drugs. Rahman and colleagues (29,30) incorporated adriamycin into liposomes composed of phosphatidylcholine and cholesterol mixed with stearyl amine (positively charged) or phosphatidylserine (negatively charged). Lipsosomal incorporation may result in internalization of drug into cells by endocytosis. Use of adriamycin has been limited by its cardiac toxicity. Electron microscopic studies have demonstrated degeneration of myofirils and mitochondrial distortion, as well as a reduction in cardiac myocytes.

Pharmacokinetic studies have revealed avid uptake into heart muscle. Incorporation of adriamycin into positively charged liposomes effectively retarded the in vivo uptake of drug in cardiac tisssue when compared to free drug or drug incorporated into negatively charged lipsosmes (Figure 11). In this situation, adriamycin was preferentially concentrated in liver, spleen and lungs. Electron microscopic studies revealed that the myocytes and myofibrillar structure of cardiac muscle were well preserved. Importantly,, anti-tumor activity against murine ascitic P388 leukemia and Lewis lung carcinoma was identical whether adriamycin was administered alone or entrapped in positively charged liposomes (Figure 12). These studies and the studies presented above, suggest that liposomes may be developed to deliver their contents to specific cell types by targeting them to particular cell surface receptors.

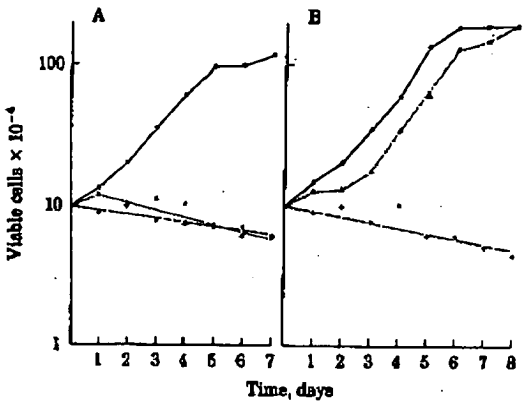

Figure 10: Specific rescue of methotrexate (MTX)-treated HBP containing cells by an asialofetuin-folinic acid conjugate. (A) PLC/PRF/5 receptor-negative cells grown in the absence of MTX (●) in 0.5 uM MTX (+), or in 0.5 uM MTX/15 uM asialofetuin-folinic acid conjugate (Δ). (B) HepG2 receptor-positive cells grown under the same conditions. (Reprinted from reference 28 with permission).

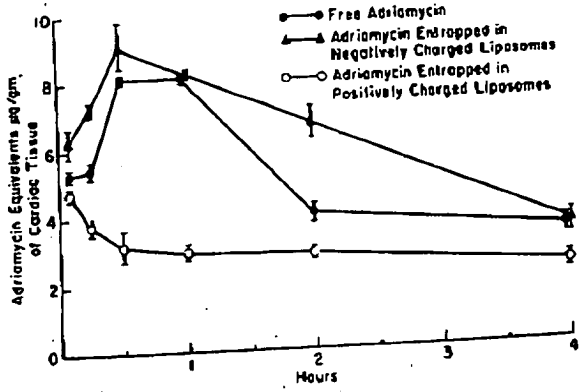

Figure 11: Adriamycin disposition in mouse heart following i.v. administration of free and liposome-entrapped drugs. (Reprinted from reference 29 with permission).

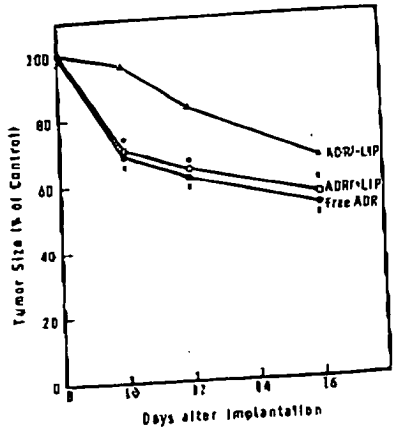

Figure 12: Treatment of mice given implants of Lewis lung carcinoma. Adriamycin (4 mg/kg) was administered i.v. to mice on days 8, 10 and 12 after tumor implantation, as free drug (Free ADR) or drug entrapped in positive (ADR/+ LIP) or negative (ADR/-LIP) liposomes. The percentage of reduction of tumor mass was assessed by measuring the largest perpendicular diameter of the primary tumor. The asterisk indicates statistical difference from control ($P < 0.05$). (Reprinted from reference 29 with permission).

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